**Citation:**

Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, Rodriguez C, Sinha R, Calle EE. Meat consumption and risk of colorectal cancer. *JAMA*. 2005;293(2):172-82.

**PubMed ID:** 15644544

**Study Design:**

prospective cohort

**Class:**

B - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To examine the relationship between recent and long-term meat consumption and the risk of incident colon and rectal cancer.

**Inclusion Criteria:**

- Participant in the CPS II Mortality Cohort and the subset, CPS II Nutrition Cohort study.
- Age 50 to 74 years.
- Residing in a state with population-based cancer registry.

**Exclusion Criteria:**

- Persons who were not known to be deceased but failed to respond to the 1997, 1999, and 2001 questionnaires (3.7%).
- Report of colon or rectal cancer not verified by pathology report or death certificate (0.3%).
- Report at baseline of a personal history of colon or rectal cancer (1.5%).
- Reported uninterpretable or missing data on meat consumption in 1982 (4.7%).
- Completed less than 85% of the food section of the 1992/1993 questionnaire.
- Reported implausibly high or low energy intake (9.1%).

**Description of Study Protocol:**

**Recruitment**

- Participant in the CPS II Mortality Cohort and the subset Nutrition Cohort.

**Design**

- Cohort

**Blinding used**

N/A

**Intervention**

- None
- Meat intake: dietary assessment in 1992/1993 was based on a 68-item modified Block food-frequency questionnaire (FFQ). Nutrient values were estimated using the Dietary Analysis System version 3.8a. Consumption of each meat item in grams per week was estimated by taking the product of average frequency per week, number of grams in a medium serving, and serving size (0.5 for small, 1.0 for medium, and 1.5 for large). Intake of red meat, poultry and fish, and processed meat (g/wk) was computed by summing across meat items that contributed to each meat group and categorizing by quintile. The lowest quintile of intake served as the referent group for analyses. The FFQ was validated among 441 Nutrition Cohort members who completed four 24-hour dietary recall interviews and a repeat FFQ. Long-term consumption was examined by considering consumption reported in 1982 and in 1992/1993. Consumption at each time point was categorized into tertiles (low, moderate, high) and participants were classified as low intake in 1982 and 1992/1993 (referent group), high intake in 1982 and 1992/1993, and all other combinations of intake over time.

**Statistical Analysis**

- Colon and rectal cancer incidence rate ratios (RRs) and 95% CIs by meat intake were estimated using Cox proportional hazards regression modeling.
- *P* values for linear trend were estimated by modeling meat intake (g/wk) using the median value within quintiles; these results were similar when modeled as continuous variables.
- To obtain P values and confidence limits, we treated the disease outcome as though it were a random variable that changed over time.
- Potential confounders were chosen based on a priori considerations and on the observed association with colon or rectal cancer and meat intake.
- For each meat variable, 3 models were constructed stratified by single year of age, controlling for other covariates.
- Model 1 included total energy (continuous); Model 2 included total energy, education (some high school, high school graduate, some college or trade school, college graduate or postgraduate work, or unknown), body mass index calculated as weight in kilograms divided by the square of height in meters in 1992/1993 (<18.5, 18.5-24.9, 25.0-29.9, 30.0-39.9, >/=40.0, or unknown), cigarette smoking in 1992/1993 (never, former, current, ever smoker not specified, or unknown), recreational physical activity in 1992/1993 (none, hours per week of walking, or walking plus other activities), multivitamin use in 1982 (none, current user, or unknown), aspirin use in 1982 and 1992 (nonuser in 1982 and 1992, >/= 15 days per month in 1982 and 1992, < 15 days per month in 1982 or 1992, or unknown at either time point), intake of wine (none, any), beer (none, any), and liquor (none, any), and hormone therapy use in 1992/1993 among women (nonuser, former user, current user, ever user not specified, or unknown); Model 3 included all covariates in model 2 plus intake of fruits 1992/1993 (quintiles), vegetables in 1982 (quintiles), and high fiber grain foods in 1982 (quintiles). Models of men and women combined also included a term for sex.
- Family history of colorectal cancer reported in 1982 was examined and excluded as a potential confounder; no information on family history of colorectal cancer was available in 1992/1993.

- Results of models including age and energy were similar to those from models including only age or age plus energy in quintiles.
- In a subanalysis of meat consumption reported in 1992/1993, we examined quintiles of energy-adjusted intake of red meat, poultry and fish, and processed meat based on the residual method.
- How the association with each type of meat was affected was also examined when controlling for other types of meat; no substantial difference was observed in these analyses (results were not shown).
- The proportional hazard assumption for each meat intake variable was tested in relation to colon or rectal cancer using the likelihood ratio test, comparing models with and without product terms for meat consumption (quintiles) and follow-up time (years).
- Evaluated effect modification of the RR for colon and rectal cancer in relation to meat consumption by other covariates using the likelihood ratio test comparing models with and without interaction terms.
- The Wald statistic was used to test for homogeneity of the RR for proximal and distal colon cancers.
- All P values were 2-sided and considered significant at $P<0.05$.
- All analyses were conducted using SAS version 9.0.

**Data Collection Summary:**

**Timing of Measurements**

- Questionnaires conducted in 1982 and 1992/1993.

**Dependent Variables**

- Incident of Colon or Rectal cancer

**Independent Variables**

- Long-term meat consumption

**Control Variables**

- Potential confounders were chosen based on a priori considerations and on the observed association with colon or rectal cancer and meat intake.
- total energy
- education
- body mass index
- cigarette smoking
- recreational physical activity
- multivitamin use
- aspirin use
- intake of wine, beer, liquor
- hormone therapy use
- intake of fruits, vegetables and high fiber grain foods
- family history of colorectal cancer
- age
- sex

**Description of Actual Data Sample:**

**Initial N**:

- 1.2 million adults in the CPS II Mortality Cohort
- CPS II Nutrition Cohort comprised 86,404 men and 97,786 women

**Attrition (final N):**

- After exclusions, the analytic cohort included 69,664 men and 78,946 women, representing 81% of the CPS II Nutrition Cohort.

**Age**: The median age at the CPS II Nutrition Cohort enrollment was 63 years.

**Ethnicity**: 2-3% of the cohort were nonwhite

**Other relevant demographics**: (from Table 1 characteristics in the year before study enrollment)

- Education, none beyond high school ranged from 17-44%
- No recreational physical activity in 1992 ranged from 6-18%
- Current cigarette smoking in 1992 ranged from 4-14%
- Any beer consumption in 1992 ranged from 12-51% (almost 3 times greater in men than in women)
- Any wine consumption in 1992 ranged from 32-45%
- Any liquor consumption in 1992 ranged from 20-43% (34-43 for men; 20-31 for women)
- Multivitamin use in 1982 ranged from 26-46% (26-36% for men; 36-46% for women)
- Aspirin use of >/=15 d/mo in 1982 ranged from 8-10%
- Current use of hormone therapy in 1992 ranged from 29-35%
- Median daily energy intake in 1992 ranged from 1061-2387 calories (1322-2387 for men; 1061-1749 for women)
- <1 serving/d of fruits in 1992 ranged from 18-27%
- Low or no vegetable intake in 1982 ranged from 14-24%
- No intake of high-fiber grain foods in 1982 ranged from 15-27%

**Anthropometrics**

- Median BMI in 1992 ranged from 23-27

**Location**:

- The CPS II Mortality Cohort recruited men and women from all 50 states, Puerto Rico, and the District of Columbia

**Summary of Results:**

**Key Findings:**

Meat Consumption and Colon Cancer Incidence

- A 10-fold difference was observed between the lowest and highest quintiles of red meat in men and a 17-fold difference in women.
- For men the quintile range of intake was </= 180 to > 800 g/wk, while for women it was </= 90 to > 560 g/wk.

- Men reported greater consumption of red and processed meat than did women; median intake 427 g/wk and 274 g/wk for red meat among men and women, respectively, and 95 g/wk and 43 g/wk for processed meat, respectively.
- There was little variation in the consumption of poultry and fish by quintiles of red meat intake.
- Men also reported sustantially higher intake of red and processed meats in 1982 than did women (data was not shown).
- Approximately half of the men and women in the top tertile for consumption of red or processed meat in 1982 were also in the highest tertile in 1992/1993 (data was not shown). The absolute levels of meat consumption in 1982 could not be compared with consumption in 1992/1993 due to differences in the questionnaires.
- Men and women who reported higher intake of red meat in 1992/1993 were more likely to report lower educational attainment, no recreational physical activity, higher body mass index, current cigarette smoking, beer and liquor drinking, higher total daily energy intake, low fruit intake in 1992/1993, and little or no intake of vegetables or high-fiber grain foods in 1982 compared with those with lower red meat intake.
- Men and women who reported lower red meat intake tended to report multivitamin use in 1982, wine drinking, and (in women) use of hormone therapy in 1992/1993.
- Higher intake of red and processed meat was associated with higher colon cancer risk in mean and women in models that adjusted only for age and eneryg intake (model 1). However, the positive associations were attenuated in analyses (model 2) that further adjusted for nondietary factors. Further adjustment for dietary factors (model 3) had little effect on the RR estimates.
- No association was observed between colon cancer incidence and consumption frequency of beef, pork, or lamb as a main dish, or with reported preference for red meat doneness.
- Higher consumption of poultry and fish was inversely associated with colon cancer risk in women but not men. Adjustment for covariates other than energy attenuated the association. Among women, the inverse relationship remained statistically significant (P=0.03 for trend).
- The positive association between colon cancer risk and ratio of red meat-to-poultry and fish intake was also stronger in women than men. The trend test for the ratio of red meat-to-poultry and fish intake was statistically significant in men, women and both sexes combined.

Proximal and Distal Colon Cancer, and Rectal Cancer

- After covariate adjustment, no consistent association was observed between consumption of red meat, poultry and fish, or processed meat as reported at a single time point and cancer of either subsite of the colon.
- Men and women in the second to fifth quintiles of red meat intake had higher risk of rectal cancer compared with those in the lowest quintile, particularly those individuals in the highest quintile (RR, 1.71; 95% CI, 1.15-2.52; P=0.07 for trend). This association was observed primarily with cancers of the rectosigmoid junction (RR, 2.40; 95% CI, 1.30-4.43) with risk increasing significantly with the amount of red meat consumed (P=0.02 for trend).

Energy-Adjusted Meat Intake

- Analyses using energy-adjusted meat intake reported in 1992/1993 yielded results similar to those using meat intake (g/wk) with few exceptions.
- Compared with risk estimates derived from nonenergy-adjusted meat intake, the association between colon cancer and consumption of processed meat (RR, 1.35; 95% CI, 1.04-1.77; highest to lowest quintile, P+0.02 for trend) became stronger in men, although the

association between rectal cancer and red meat intake (RR, 1.31; 95% CI, 0.96-1.79; P+0.03 for trend) was attenuated in men and women combined.

Long-term Meat Consumption

- Prolonged high consumption of red meat was associated with a statistically nonsignificant increased risk of distal colon cancer (RR, 1.29; 95% CI, 0.88-1.89).
- The most consistent associations were observed between distal colon cancer and prolonged high intake of processed meat (RR, 1.50; 95% CI, 1.04-2.17), and ratio of red meat to poultry and fish (RR, 1.53; 95% CI, 1.08-2.18) compared with persons with prolonged low intake.
- Long-term high intake of poultry and fish was marginally associated with lower risk of proximal (RR, 0.77; 95% CI, 0.59-1.02) and distal (RR, 0.70; 95% CI, 0.50-0.99) colon cancer.
- Red meat consumption was marginally associated with higher risk of rectal cancer (RR, 1.43; 95% CI, 1.99-2.05); this association was somewhat stronger for cancers of the rectosigmoid junction (RR, 1.75; 95% CI, 1.04-2.96) than for cancer of the rectum (RR, 1.31; 95% CI, 0.79-2.15).

Effect Modification

- No statistically significant interaction was observed between meat consumption and other known risk factors for colon or rectal cancer on a multiplicative scale.

**Author Conclusion:**

Limitations as cited by authors.

- Measurement error inherent in studies based on FFQs.
- The 1982 questionnaire did not assess the number of servings of meat per day and could not differentiate persons who ate multiple servings from those who ate meat only once per day; we were also unable to estimate total energy intake from the 1982 questionnaire.
- No information on meat cooking methods to estimate exposure to heterocyclic amines or other specific carcinogens produced from pyrolysis of meat; the reliance on self-reported data on preference for doneness of meat was likely crude proxy of the relevant exposures.
- No information on family history of colorectal cancer from the 1992/1993 questionnaire to update this important variable, which could potentially modify the association between meat intake and risk of colorectal cancer.
- No information was collected on examination by sigmoidoscopy, colonoscopy, or fecal occult blood test in either the 1982 or 1992/1993 questionnaires. However, in 1997, persons who reported long-term high consumption of red meat were less likely (23%) to have had endoscopy for screening than those persons who reported long-term low intake of red meat (34%).

The results demonstrate the potential value of examining long-term meat consumption in assessing cancer risk and strengthen the evidence that prolonged high consumption of red and processed meat may increase the risk of cancer in the distal portion of the large intestine.

***Reviewer Comments:***

*Research Design and Implementation Criteria Checklist: Primary Research*

## Relevance Questions

| | | |
|---|---|---|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | N/A |

## Validity Questions

| | | |
|---|---|---|
| **1.** | **Was the research question clearly stated?** | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |
| 1.3. | Were the target population and setting specified? | Yes |
| **2.** | **Was the selection of study subjects/patients free from bias?** | Yes |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |
| 2.2. | Were criteria applied equally to all study groups? | N/A |
| 2.3. | Were health, demographics, and other characteristics of subjects described? | Yes |
| 2.4. | Were the subjects/patients a representative sample of the relevant population? | ??? |
| **3.** | **Were study groups comparable?** | Yes |
| 3.1. | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) | Yes |
| 3.2. | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? | N/A |
| 3.3. | Were concurrent controls used? (Concurrent preferred over historical controls.) | N/A |

| | | |
|---|---|---|
| 3.4. | If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? | Yes |
| 3.5. | If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) | N/A |
| 3.6. | If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")? | N/A |
| **4.** | **Was method of handling withdrawals described?** | Yes |
| 4.1. | Were follow-up methods described and the same for all groups? | N/A |
| 4.2. | Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) | N/A |
| 4.3. | Were all enrolled subjects/patients (in the original sample) accounted for? | Yes |
| 4.4. | Were reasons for withdrawals similar across groups? | N/A |
| 4.5. | If diagnostic test, was decision to perform reference test not dependent on results of test under study? | N/A |
| **5.** | **Was blinding used to prevent introduction of bias?** | ??? |
| 5.1. | In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? | N/A |
| 5.2. | Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) | N/A |
| 5.3. | In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? | ??? |
| 5.4. | In case control study, was case definition explicit and case ascertainment not influenced by exposure status? | N/A |
| 5.5. | In diagnostic study, were test results blinded to patient history and other test results? | N/A |
| **6.** | **Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?** | Yes |
| 6.1. | In RCT or other intervention trial, were protocols described for all regimens studied? | N/A |
| 6.2. | In observational study, were interventions, study settings, and clinicians/provider described? | Yes |

| | | |
|---|---|---|
| 6.3. | Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? | Yes |
| 6.4. | Was the amount of exposure and, if relevant, subject/patient compliance measured? | Yes |
| 6.5. | Were co-interventions (e.g., ancillary treatments, other therapies) described? | N/A |
| 6.6. | Were extra or unplanned treatments described? | N/A |
| 6.7. | Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? | Yes |
| 6.8. | In diagnostic study, were details of test administration and replication sufficient? | N/A |
| **7.** | **Were outcomes clearly defined and the measurements valid and reliable?** | Yes |
| 7.1. | Were primary and secondary endpoints described and relevant to the question? | Yes |
| 7.2. | Were nutrition measures appropriate to question and outcomes of concern? | Yes |
| 7.3. | Was the period of follow-up long enough for important outcome(s) to occur? | Yes |
| 7.4. | Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? | Yes |
| 7.5. | Was the measurement of effect at an appropriate level of precision? | Yes |
| 7.6. | Were other factors accounted for (measured) that could affect outcomes? | Yes |
| 7.7. | Were the measurements conducted consistently across groups? | Yes |
| **8.** | **Was the statistical analysis appropriate for the study design and type of outcome indicators?** | Yes |
| 8.1. | Were statistical analyses adequately described and the results reported appropriately? | Yes |
| 8.2. | Were correct statistical tests used and assumptions of test not violated? | Yes |
| 8.3. | Were statistics reported with levels of significance and/or confidence intervals? | Yes |
| 8.4. | Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? | N/A |
| 8.5. | Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? | Yes |
| 8.6. | Was clinical significance as well as statistical significance reported? | Yes |

| | | |
|---|---|---|
| 8.7. | If negative findings, was a power calculation reported to address type 2 error? | N/A |
| **9.** | **Are conclusions supported by results with biases and limitations taken into consideration?** | Yes |
| 9.1. | Is there a discussion of findings? | Yes |
| 9.2. | Are biases and study limitations identified and discussed? | Yes |
| **10.** | **Is bias due to study's funding or sponsorship unlikely?** | Yes |
| 10.1. | Were sources of funding and investigators' affiliations described? | Yes |
| 10.2. | Was the study free from apparent conflict of interest? | Yes |